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MINIATURE PIG PERFORMANCE AFTER FRACTIONATED DOSES OF IONIZING RADIATION

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Atomic Support Agency
Bethesda, Maryland

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MINIATURE PIG PERFORMANCE AFTER FRACTIONATED DOSES OF IONIZING RADIATION

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FOREWORD
(Nontechnical summary)

It is generally recognized that biological effects of radiation are reduced when the radiation is delivered in several fractions instead of in a single uninterrupted dose. Although reduced responses to radiation have been most frequently observed when doses in the lethal range or below were fractionated, it has also been demonstrated that the response is reduced when supralethal doses are fractionated.

The behavior of miniature pigs, monkeys, and dogs after supralethal doses of ionizing radiation has been extensively studied. Over a wide range of such doses, the pig and monkey experienced a period of early transient incapacitation shortly after irradiation but recovered to perform at relatively normal levels until becoming permanently incapacitated a few hours before death. The dog did not experience transitory incapacitation. Instead, its condition deteriorated until permanent incapacitation occurred shortly before death.

The purpose of this study was to determine if trained miniature pigs would experience less incapacitation and performance decrement when the doses were fractionated rather than delivered in a single pulse.

Miniature pigs received either unfractionated (6500, 8600, 11,600, or 13,000 rads) or fractionated (6800, 8500, 11,000, or 13,300 rads) doses of pulsed mixed gamma-neutron radiation. The fractionated doses were delivered as two equal fractions 5 hours apart.

The pigs were trained to traverse a shuttlebox when presented with visual and auditory cues and their postirradiation performance was tested at specified intervals until death.

Miniature pig performance after the second half of the fractionated dose was similar to or better than the performance observed after the first half of the dose. The pig's performance was markedly better when the dose was fractionated than when it was unfractionated; early transient incapacitation was shorter, and acceptable performance was achieved earlier and lasted longer. Also, mean survival times for the pigs that received fractionated doses were longer.

Permanent performance decrement and incapacitation occurred immediately in several pigs at all dose levels when the dose was unfractionated. When the dose was fractionated, however, only at the highest dose of 13,300 rads were any pigs similarly affected.

The results of this study indicate that fractionated doses of pulsed mixed gamma-neutron radiation affect miniature pigs much less severely than do equivalent unfractionated doses.

ABSTRACT

Miniature pigs were trained to traverse on cue a two-chambered shuttlebox. The pigs received either unfractionated (6500, 8600, 11,600, or 13,000 rads) or fractionated (6800, 8500, 11,000, or 13,300 rads) doses of pulsed mixed gamma-neutron radiation. The fractionated doses were delivered as two equal fractions 5 hours apart. Miniature pig performance after the second half of the fractionated dose was similar to or better than the performance observed after the first half of the dose. The pig's performance was markedly better when the dose was fractionated than when it was unfractionated; early transient incapacitation was shorter, and acceptable performance was achieved earlier and lasted longer. Also, mean survival times of the pigs that received fractionated doses were longer. Possible mechanisms which may be responsible for the reduced effectiveness of the fractionated doses are discussed.

I. INTRODUCTION

It is generally recognized that the biological effects of whole-body irradiation are reduced when the radiation is delivered in several fractions instead of in a single uninterrupted dose. These reduced responses to radiation have been most frequently observed in the lethal dose range or below.[1,7,8]

It has also been demonstrated that the radiation response is reduced when supralethal doses are fractionated.[2,11,12] Although death was inevitable, survival time in mice, rats, guinea pigs, and hamsters was significantly increased when these doses were fractionated.

The behavior of miniature pigs, monkeys, and dogs after supralethal doses of ionizing radiation has been extensively studied.[3,4,6,9] Over a wide range of such doses the pig and monkey experienced early transient incapacitation (ETI) shortly after irradiation but recovered to perform at relatively normal levels until becoming permanently incapacitated a few hours before death. The dog did not experience ETI. Instead, its condition gradually deteriorated until it was permanently incapacitated shortly before death.

The purpose of this study was to determine if trained miniature pigs would experience less incapacitation and performance decrement when the mixed gamma-neutron radiation doses were fractionated rather than delivered in a single pulse.

II. PROCEDURES

The subjects were 48 miniature pigs (female, male, and barrow) of the Hormel, Hormel-Hanford, and Rosemount strains. They weighed 20 to 45 kg and were 17 to 24 cm thick at the shoulders when irradiated.

The pigs were exposed unilaterally to the left side to a pulse of mixed gamma-neutron radiation from the AFRRI-TRIGA reactor.[9] They received either unfractionated (6500, 8600, 11,600, or 13,000 rads) or fractionated (6800, 8500, 11,000, or 13,300 rads) doses. The doses reported are to the midline of the trunk of the pig. The ratio of head to trunk midline tissue doses was approximately 1.5. The fractionated doses were delivered as two equal (± 5 percent) fractions 5 hours apart. The dose to individual pigs within groups varied less than 6 percent from the group mean. Since the ratio of maximum to minimum dose exceeded 1.3, the irradiations were Class B nonuniform as defined in the International Commission on Radiological Units and Measurements Report 10e.

The exposure configuration was the same as described in another report.[3] The midline of each pig was about 100 cm from the vertical center line of the reactor core for all pigs except those which received 11,600 and 13,000 rads as an unfractionated dose. To obtain these doses the source to animal distance had to be decreased; the six pigs that received 11,600 rads and two of the animals (pigs 44 and 45) that received 13,000 rads were positioned 80 cm and the other four animals that received 13,000 rads (pigs 43, 46, 47 and 48) were placed 44 cm from the core center line. All doses were calculated by previously reported methods.[3]

The pigs were trained by shock avoidance conditioning to traverse a two-chambered shuttlebox.[3] During each trial the pigs had 6 seconds to cross the shuttlebox after visual and auditory cues were presented, 4 seconds to cross after shock was initiated, and 3 seconds to rest. If the pigs crossed the shuttlebox before shock was initiated, they were credited with an avoidance. If the pigs crossed after shock was

initiated, they were credited with an escape. A failure was scored if the pigs did not avoid or escape. Before irradiation, each pig was trained to a minimum performance criterion of 90 percent avoidance.

Each pig was released into the shuttlebox immediately after irradiation and, with the unfractionated doses, was tested at 0, 2-1/2, 5, 7-1/2, 10, 15, 20, 25, 30, and 45 minutes, at each hour postirradiation for 8 hours, and at 2-hour intervals thereafter until death. After receiving the first half of the fractionated dose, the animals were tested on the same schedule through the fourth hour after irradiation. At 5 hours, they were replaced in the exposure configuration, given the second half of the fractionated dose, and starting again at time zero, tested on the established schedule until death. Each postirradiation test period consisted of 10 trials. Survival time was defined as the time from delivery of the unfractionated dose or of the second half of the fractionated dose to death.

III. RESULTS

Miniature pig performance after fractionated and unfractionated doses of radiation is summarized in Tables I-IV and in Figure 1. Survival times are given in Table V.

A pig was considered incapacitated when it did not cross the shuttlebox in two or more consecutive trials. If a pig did not fail two or more consecutive trials, but was unable to achieve the 90 percent avoidance level required for acceptable performance in a given test period, it was considered to be in the performance decrement category.

Miniature pig performance after the second half of the fractionated dose was similar to or better than the performance observed after the first half of the dose (Tables I-III).

The performance of the miniature pigs was markedly better when the dose of radiation was received in two equal fractions rather than in a single pulse; ETI was

Table I. Duration of ETI in Miniature Pigs After Fractionated and Unfractionated Doses of Radiation*

Pig #	Fractionated dose		Pig #	Unfractionated dose
	Fraction 1	Fraction 2		
	6800 rads			6500 rads
1	0	0	25	5
2	17	6	26	30
3	21	12	27	15
4	1	0	28	23
5	0	0	29	14
6	17	0	30	16
	8500 rads			8600 rads
7	0	0	31	30
8	22	5	32	40
9	0	0	33	240
10	1	1	34	10
11	1	0	35	60
12	0	0	36	9
	11,000 rads			11,600 rads
13	2	1	37	60
14	1	4	38	15
15	11	1	39	10.5
16	2	0	40	†
17	1	1	41	26
18	21	6	42	60
	13,300 rads			13,000 rads
19	37	26	43	†
20	22	16	44	40
21	†	†	45	†
22	1	0	46	†
23	38	16	47	†
24	20	7.5	48	40

* All times are in minutes
† Permanently incapacitated

Table II. Onset of Acceptable Performance in Miniature Pigs After Fractionated and Unfractionated Doses of Radiation*

Pig #	Fractionated dose		Pig #	Unfractionated dose
	Fraction 1	Fraction 2		
	6800 rads			6500 rads
1	2.5	12.5	25	30
2	25	20	26	45
3	180	20	27	30
4	20	45	28	†
5	10	7.5	29	20
6	20	12.5	30	20
	8500 rads			8600 rads
7	10	10	31	120
8	25	15	32	†
9	7.5	5	33	†
10	10	5	34	15
11	10	5	35	†
12	5	0	36	20
	11,000 rads			11,600 rads
13	10	10	37	120
14	15	5	38	20
15	20	5	39	15
16	15	15	40	‡
17	15	10	41	90
18	120	15	42	240
	13,300 rads			13,000 rads
19	180	180	43	‡
20	†	†	44	†
21	‡	‡	45	‡
22	20	10	46	‡
23	180	†	47	‡
24	30	†	48	†

* Proficiency of 90 percent avoidance; time expressed in minutes postirradiation
† After ETI animal was in performance decrement until permanently incapacitated
‡ Permanently incapacitated

shorter (Table I) and acceptable performance was achieved earlier after irradiation (Table II). The better performance is reflected by the greater number of avoidances attained by the pigs during the first hour after the fractionated doses (Table III). Pigs that received fractionated doses also performed at acceptable levels for longer periods (Table IV).

Table III. Number of Avoidances Attained by Miniature Pigs During the First Hour After Fractionated and Unfractionated Doses of Radiation (110 Possible)

Pig #	Fractionated dose		Pig #	Unfractionated dose
	Fraction 1	Fraction 2		
	6800 rads			6500 rads
1	100	94	25	55
2	44	75	26	26
3	18	59	27	45
4	73	53	28	0
5	88	102	29	52
6	57	84	30	53
	8500 rads			8600 rads
7	91	98	31	18
8	36	81	32	2
9	93	102	33	0
10	94	96	34	62
11	96	105	35	1
12	104	103	36	58
	11,000 rads			11,600 rads
13	75	83	37	0
14	96	91	38	50
15	55	94	39	57
16	74	68	40	0
17	73	91	41	18
18	27	69	42	0
	13,300 rads			13,000 rads
19	15	18	43	0
20	3	4	44	9
21	0	0	45	0
22	70	97	46	0
23	7	23	47	0
24	41	19	48	1

Table IV. Duration of Acceptable Performance in Miniature Pigs After Fractionated and Unfractionated Doses of Radiation*

Pig #	Fractionated dose	Pig #	Unfractionated dose
	6800 rads		6500 rads
1	86	25	46
2	64	26	69
3	48	27	32
4	60	28	0†
5	58	29	44
6	68	30	66
	8500 rads		8600 rads
7	58	31	16
8	98	32	0†
9	48	33	0†
10	90	34	12
11	86	35	0†
12	36	36	60
	11,000 rads		11,600 rads
13	52	37	12
14	30	38	16
15	38	39	14
16	18	40	0‡
17	66	41	4
18	44	42	6
	13,300 rads		13,000 rads
19	5	43	0‡
20	0†	44	0†
21	0‡	45	0‡
22	24	46	0‡
23	0†	47	0‡
24	0†	48	0†

*All times are in hours
†After ETI animal was in performance decrement until permanently incapacitated
‡Permanently incapacitated

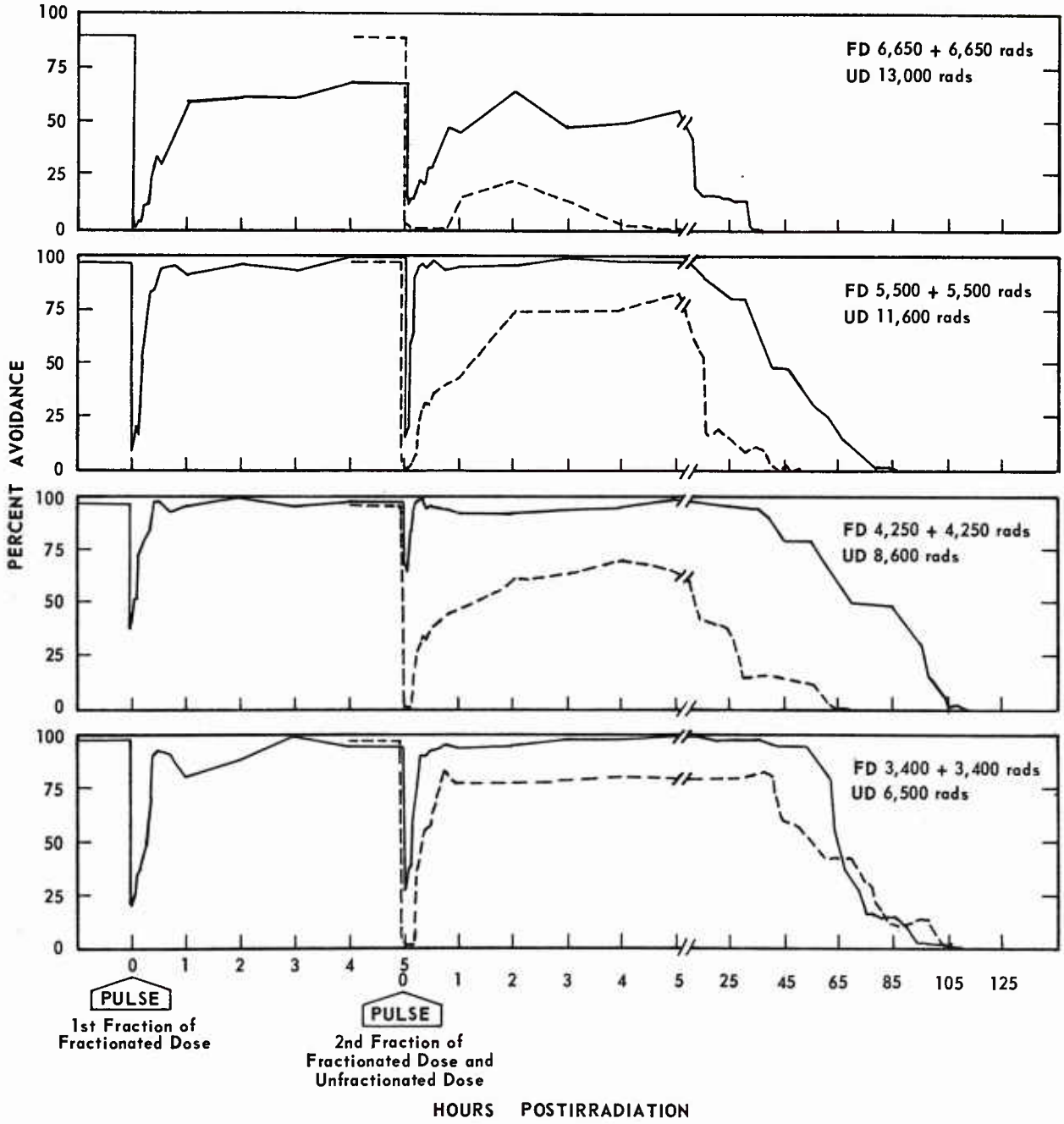

Figure 1. Average avoidance response of miniature pigs after unfractionated and fractionated doses of radiation. The curves in each dose group represent the average performance of six pigs.
Unfractionated dose (UD) ----- Fractionated dose (FD) ——

Table V. Survival Times of Miniature Pigs After Fractionated and Unfractionated Doses of Radiation*

Pig #	Fractionated dose	Pig #	Unfractionated dose
	6800 rads		6500 rads
1	110	25	60
2	76	26	107
3	77	27	83
4	71	28	0.75
5	64	29	53
6	77	30	80
Mean	79	Mean	64
	8500 rads		8600 rads
7	74	31	32
8	113	32	8.5
9	64	33	20
10	103	34	39
11	107	35	1.5
12	50	36	71
Mean	85	Mean	29
	11,000 rads		11,600 rads
13	66	37	31
14	36	38	49
15	45	39	23
16	28	40	0.25
17	88	41	12.5
18	64	42	21
Mean	54	Mean	23
	13,300 rads		13,000 rads
19	13	43	0.3
20	13.5	44	2.5
21	12	45	1.1
22	36	46	1.0
23	21	47	5.5
24	8.5	48	7.5
Mean	17	Mean	3

* All times are in hours postirradiation

All pigs that received unfractionated doses convulsed and suffered ETI or permanent incapacitation immediately after irradiation. Conversely, 9 of the 24 pigs that received fractionated doses suffered no convulsions or immediate incapacitation, and ETI lasted only 1 minute or less in four others. When doses were unfractionated, permanent performance decrement or incapacitation immediately after irradiation occurred at all dose levels. When the dose was fractionated, such severe behavioral changes were observed only after 13,300 rads.

Pigs that received fractionated doses had longer mean survival times than their counterparts who received equivalent unfractionated doses (Table V). Only one pig died in less than 10 hours after receiving a fractionated dose, whereas 10 pigs died within this period after receiving unfractionated doses.

IV. DISCUSSION

The results of this study indicate that the biological effects of pulsed mixed gamma-neutron radiations are reduced when the dose is delivered in two fractions

instead of in a single pulse. Not only did the pigs that received fractionated doses have less severe ETI and perform at an acceptable level sooner after irradiation, they also maintained this higher level of performance for a longer period and generally survived longer than animals that received equivalent unfractionated doses. In a similar study with the monkey (Macaca mulatta) better performance and a tendency toward longer survival times were observed when a 5000-rad dose was delivered in two 2500-rad fractions instead of in a single pulse.[5]

The ability of animals to recover from relatively low doses of radiation in which cellular proliferation is the main factor involved in repair has been extensively studied.[1,7,8] However, the concept of some type of recovery or activation of some protective mechanism at supralethal doses has also been proposed.[2,11,12] Although some repair of radiation injury could have occurred in the 5-hour period between delivery of the two dose fractions, other mechanisms may have increased the resistance of the animals to additional irradiation. The possibility also exists that a given level of performance decrement is encountered only when a certain radiation threshold dose is delivered within a limited time period and that these thresholds were not exceeded when the doses were fractionated.

As each additional fraction of a dose is delivered, the effect on the animal might be expected to increase. This was generally not observed in the present study. Performance after the second half of the fractionated dose was similar to or better than the performance observed after the first half of the dose. The first dose fraction appears to have conditioned the animals; physiological systems were apparently stressed and homeostatic mechanisms activated to assist the animals in resisting

additional insults. Thus, the pigs may have been partially refractory to the additional radiation.

Although several physiological systems are most likely involved in the ability of the pigs to resist further radiation injury, one may be of primary importance. Yuhas has speculated that unique mechanisms within the central nervous system are involved in the apparent recovery of animals after fractionated supralethal doses of radiation.[11,12] Since radiation damage to the head has been shown to be the primary cause of ETI and early death in pigs,[10] it is quite likely that reduced effectiveness of the fractionated dose was brought about by recovery which occurred in the central nervous system.

The significant increase in mean survival time after fractionated doses of 8500, 11,000, and 13,300 rads indicates that the central nervous system contribution to death is reduced. Similar increases in survival time were observed in head-shielded pigs.[10] Failure to observe a significant increase in pig survival time after a fractionated dose of 6800 rads suggests that, at this dose, the central nervous system is not affected severely enough to be the major cause of death.

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Miniature pigs were trained to traverse on cue a two-chambered shuttlebox. The pigs received either unfractionated (6500, 8600, 11,600, or 13,000 rads) or fractionated (6800, 8500, 11,000, or 13,300 rads) doses of pulsed mixed gamma-neutron radiation. The fractionated doses were delivered as two equal fractions 5 hours apart. Miniature pig performance after the second half of the fractionated dose was similar to or better than the performance observed after the first half of the dose. The pig's performance was markedly better when the dose was fractionated than when it was unfractionated; early transient incapacitation was shorter, and acceptable performance was achieved earlier and lasted longer. Also, mean survival times of the pigs that received fractionated doses were longer. Possible mechanisms which may be responsible for the reduced effectiveness of the fractionated doses are discussed.

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